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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/010,914	12/05/2001	Shanker Gupta	9022.30	6114

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EXAMINER	
CHOI, FRANK I	
ART UNIT	**PAPER NUMBER**
1616	

DATE MAILED: 03/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/010,914	GUPTA ET AL.	
	Examiner	Art Unit	
	Frank I. Choi	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/29/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Specification

Pg. 10, lines 13,14, please update reference to the cited application by indicating that it is now Patent No. 6,368,831.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 18, 19, 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for non-ionic surfactants, does not reasonably provide enablement for egg phospholipids as nonionic surfactants. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicant lists egg phospholipids as non-ionic surfactants, however, the prior art cited indicates that egg phospholipids are ionic surfactants. Applicant does not appear to show how the egg phospholipids are nonionic, as such, it appears that a skilled artisan would be required to do undue experimentation in order to make and/or use a non-ionic egg phospholipid.

Examiner notes that Applicant has provides evidence supporting its assertions that ionic egg phospholipids have a neutral charge at the pH range of 5-10. However, the terms anionic, cationic, zwitterionic and non-ionic in relation to surfactants are terms of art identifying specific types of surfactants (See generally, Chen et al., Column 9, lines 1-15). As such, the fact that an ionic surfactant may have a neutral charge over a specified pH range does not make the ionic

surfactant a non-ionic surfactant. Based on Applicant's declaration, at best, the egg phospholipids over the pH range of 5-10 could be described as being zwitterionic. However, zwitterionic is not the same as non-ionic. The egg phospholipids over the pH range of 5-10 are still ionic surfactants, it just that the ionic charges cancel each other such that the compound is neutral. For the same reason that an imidazoline betaine surfactant would not be considered to be a non-ionic surfactant, an egg phospholipid surfactant cannot be considered to be non-ionic. Applicant's reliance on Young et al. as identifying egg phospholipids as non-ionic surfactants is misplaced. In the first instance, the phospholipids are not identified as non-ionic surfactants and are not part of the list of non-ionic surfactants (Young et al., pg. 2, Figure 1). Young et al. discloses that the phospholipids were mixed with small amounts of micelle-forming surfactants, which are listed in Figure 1, to enhance fluidity of the surfactant bilayers (Young et al., Pg. 2). Young et al. further discloses that the nonionic surfactants can act to make the vesicle bilayer more fluid (Young et al., Pg. 6). As such, a clear reading of the Young et al. reference is that the non-ionic surfactants do not include the phospholipids but are added to the phospholipids to improve the properties of the phospholipid vesicles.

Claims 29-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Specification only discloses egg phospholipids in the context of being a non-ionic surfactant. As such, according to the Specification the egg phospholipid would have to be non-ionic. However, as indicated above, in the context of an enablement rejection, the

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Applicant lists egg phospholipids as non-ionic surfactants, however, the prior art cited indicates that egg phospholipids are ionic surfactants. Applicant does not appear to show how the egg phospholipids are nonionic, as such, it appears that a skilled artisan would be required to do undue experimentation in order to make and/or use a non-ionic egg phospholipid. Since non-ionic egg phospholipids are non-enabled and Applicant does not describe the use of other forms of egg phospholipids other than non-ionic, Applicant's insertion of egg phospholipids per se constitutes new matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 11-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lopez-Berestein et al. (US 2002/0143062) in view of Chen et al. (US 6,267,985), Lambert et al. (US Pat. 6,660,286) and Shudo et al. (US 5,676,146).

Lopez-Berestein et al. discloses that as with many retinoids, N-(4-hydroxyphenyl) retinamide (4-HPR) is poorly soluble in water (Paragraph 0008). It is discloses that 4-HPR is effective in treatment of cancer (Paragraph 0014). It is disclosed that the retinoid, such as 4-HPR, is combined with a lipid, such as triglyceride fatty acid esters (Paragraphs 0076-0080). It is disclosed that the retinoid can be emulsified with a lipid and that methods of preparing lipid

emulsionis and adding additional components are well known in the art (Paragaraphs 0091-0095). It is disclosed that a lipid emulsion is a substantially permanent heterogenous liquid mixture of two or more liquids that do no normally dissolve in each other by mechanical agitation or by small amounts of additional substances known as emulsifiers, for example, one or more lipids can be added to ethanol or other suitable organic solvent which is evaporated, which resulting dried glaze of lipid is resuspended in aqueous media, such as phosphate buffered slaine, resulting in an emulsion (Paragraphs 0094, 0095). A parenteral formulation is disclosed having a pH of 7.5 to 9.0 (Paragraphs 0334,0335).

Chen et al. discloses that a wide variety of therapeutic agents are conventionally formulated in oil/water emulsion systems that take advantage of the increased solubility of many therapeutic agents in oils (triglycerides), such as soybean oil (Column 1, lines 10-33, Column 6, lines 17). It is disclosed that suitable surfactants include non-ionics, including polyethoxylated fatty acid esters, POE-POP box copolymers, and ionics, including cationic, anionic or zwitterionic, including egg lecithins, phosphatidylcholine (Column 8, lines 18-68, Columns 9, 10, Column 20, lines 54-68, Column 22, lines 43-68, Column 23, lines 33-43). It is disclosed that the therapeutic agent can be hydrophobic and can be a retinoid (Column 28, lines 40-49, Column 31, line 11). It is disclosed that solubilizers such as ethanol can be added increase the solubility of the therapeutic agent or triglyceride in the composition which then can be removed prior to providing the composition to a patient by distillation or evaporation (Column 33, lines 62-68, Column 34, lines 1-56). It is taught that small particle sizes avoid safety problems found with large particle sizes in parenteral administration (Column 40, lines 26-35).

Lambert et al. (US Pat. 6,660,286) disclose that the oils typically used for pharmaceutical emulsions include saponifiable oils from the family of triglycercides such as soybean oil, cottonseed oil, safflower oil and the like (Column 2, lines 18-27). It is disclosed that one or more surfactants, such as lecithin from egg yolks, are used to stabilize the emulsion and excipients are added to render the emulsion more biocompatible, stable and less toxic (Column 2, lines 27-31). It is disclosed that stability is influenced by that size and homogeneity of the emulsion and that the preferred emulsion consists of a suspension of sub-micron particles, with a mean droplet diameter of no greater than 200 nanometers (Column 2, lines 29-50). It is disclosed that one means of solubilizing low solubility compounds is direct solubilization in a non-aqueous milieu, for example alcohol, such as ethanol, or dimethylsulfoxide (Column 3, lines 18-20).

Shudo et al. teach that glycerine is used in pharmaceutical formulations for injection as an isotonizing agent (Column 5, lines 47-55).

The difference between the prior art and the claimed invention is that the prior art does not expressly disclose the retinide composition having the claimed components in the claimed amounts. However, the prior art amply suggests the same as the prior art teaches the used of emulsions to administer hydrophobic drugs, including retinoids, for the treatment of cancer, in the form of emulsions. Further, it would have well within the skill of and one of ordinary skill in the art would have been motivated to use a lipid, such as soy bean oil, with the expectation of increasing the solubility of the retinoid, a solvent such as ethanol with the expectation of increasing the solubility of the retinoid and/or lipid, a non-ionic surfactant with the expectation of increasing the ability of the triglyceride to solubilize the retinide. Further, it would have been

well within the skill of one of ordinary skill in the art to use various amounts of the components, including amounts falling within the claimed amounts, depending on the amount of drug, ph, tonicity, stability, solubility and clarity desired.

Examiner has duly considered Applicant's arguments but deems them unpersuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 231 USPQ 375 (Fed. Cir. 1986). Further, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 208 USPQ 871 (CCPA 1981).

The argument that liposomes are difficult to manufacture and are unstable has no bearing on the rejection herein, because, Lopez-Berestein is not being cited for its teaching of liposomes but for its teaching that preparation of emulsions are well known in the art. Examiner notes that Applicant does not cited to documents which support the above argument. Arguments of counsel cannot take the place of evidence in the record. In re Schulze, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a prima facie case of obviousness."). In any case, Grit et al. clearly indicate that with respect to phospholipids based liposomes that stability can be maximized by various techniques (See entire reference). Further, any purported difficulties in manufacturing

and/or stability do not overcome the fact that the prior art discloses how to make and use liposomes.

There is nothing in Lopez-Berestein et al.which indicates a failure to formulate fenretinide in a more easily manufactured and quality-controllable composition, as Lopez-Berestein et al. clearly indicates that emulsions are well within the skill of one of ordinary skill in the art. Further, Lopez-Berestein et al. does not require the use of the liposome in an emulsion, identifies liposomes as a separate embodiment of a lipid formulation and clearly indicates that the emulsion may simply contain among other components a lipid and the retinoid and aqueous media (See Lopez-Berestein et al., paragraphs 0091-0101). In any case, there is no requirement that Lopez-Berestein et al. disclose all the components of the claimed invention as the rejection is based on a combination of references.

Applicant argues that tertiarybutyl alcohol is toxic to humans, however, Applicant does not provide any evidence that tertiary butyl alcohol as used in Lopez-Berestein reference will be toxic to humans or that tertiary butyl alcohol is required in the preparation of the emulsion. In any case, the claims do not exclude the use of use of tertiary butyl alcohol and the issue of safety of tertiary butyl alcohol cannot overcome the rejection herein. See In re Jansen, 187 USPQ 743, 745,746 (CCPA 1975) (whether members of the medical community would agree or disagree as to the safety of a medical treatment cannot control the determination whether the claimed product and method would have unobvious to a person having ordinary skill in the art). In any case, Lopez-Berestein et al. does not require the use of tertiary butyl alcohol to prepare the liposomes (See paragraphs 0103-0108).

Applicant does not indicate how Chen et al. or Shudo et al. fail to teach or provide the missing elements of Lopez-Berestein et al. Since neither the fact that Lopez-Berestein et al. does not disclose all the elements of the claimed invention or the fact that Lopez-Berestein et al. discloses the use of tertiary butyl alcohol is sufficient to overcome the rejection herein, the rejection herein is maintained.

Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention has been collectively taught by the combined teachings of the references.

Conclusion

A facsimile center has been established in Technology Center 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier number for accessing the facsimile machine is 571-273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Choi whose telephone number is (571)272-0610. Examiner maintains a flexible schedule. However, Examiner may generally be reached Monday-Friday, 8:00 am – 5:30 pm (EST), except the first Friday of the each biweek which is Examiner's normally scheduled day off.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, Mr. Gary Kunz, can be reached at 571-272-0887. Additionally, Technology Center 1600's Receptionist and Customer Service can be reached at (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

FIC
March 18, 2005

S. MARK CLARDY
PATENT EXAMINER
GROUP 1200
1616